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APPLICATION NO.	FILING DATE	FIRST NAMED INVENTOR	ATTORNEY DOCKET NO.	CONFIRMATION NO.
09/988,013	11/16/2001	Shui-on Leung	18733/1082	7681

22428 7590 02/20/2004

FOLEY AND LARDNER
SUITE 500
3000 K STREET NW
WASHINGTON, DC 20007

EXAMINER	
BLANCHARD, DAVID J	
ART UNIT	**PAPER NUMBER**
1642	

DATE MAILED: 02/20/2004

Please find below and/or attached an Office communication concerning this application or proceeding.

AT

Office Action Summary	Application No.	Applicant(s)	
	09/988,013	LEUNG ET AL.	
	Examiner	Art Unit	
	David J Blanchard	1642	

-- The MAILING DATE of this communication appears on the cover sheet with the correspondence address --

Period for Reply

A SHORTENED STATUTORY PERIOD FOR REPLY IS SET TO EXPIRE 3 MONTH(S) FROM THE MAILING DATE OF THIS COMMUNICATION.

- Extensions of time may be available under the provisions of 37 CFR 1.136(a). In no event, however, may a reply be timely filed after SIX (6) MONTHS from the mailing date of this communication.
- If the period for reply specified above is less than thirty (30) days, a reply within the statutory minimum of thirty (30) days will be considered timely.
- If NO period for reply is specified above, the maximum statutory period will apply and will expire SIX (6) MONTHS from the mailing date of this communication.
- Failure to reply within the set or extended period for reply will, by statute, cause the application to become ABANDONED (35 U.S.C. § 133).
- Any reply received by the Office later than three months after the mailing date of this communication, even if timely filed, may reduce any earned patent term adjustment. See 37 CFR 1.704(b).

Status

1)☐ Responsive to communication(s) filed on _____ .

2a)☐ This action is **FINAL**. 2b)☒ This action is non-final.

3)☐ Since this application is in condition for allowance except for formal matters, prosecution as to the merits is closed in accordance with the practice under *Ex parte Quayle*, 1935 C.D. 11, 453 O.G. 213.

Disposition of Claims

4)☒ Claim(s) 25-27 is/are pending in the application.

4a) Of the above claim(s) _____ is/are withdrawn from consideration.

5)☐ Claim(s) _____ is/are allowed.

6)☒ Claim(s) 25-27 is/are rejected.

7)☐ Claim(s) _____ is/are objected to.

8)☐ Claim(s) _____ are subject to restriction and/or election requirement.

Application Papers

9)☒ The specification is objected to by the Examiner.

10)☐ The drawing(s) filed on _____ is/are: a)☐ accepted or b)☐ objected to by the Examiner.

Applicant may not request that any objection to the drawing(s) be held in abeyance. See 37 CFR 1.85(a).

11)☐ The proposed drawing correction filed on _____ is: a)☐ approved b)☐ disapproved by the Examiner.

If approved, corrected drawings are required in reply to this Office action.

12)☒ The oath or declaration is objected to by the Examiner.

Priority under 35 U.S.C. §§ 119 and 120

13)☐ Acknowledgment is made of a claim for foreign priority under 35 U.S.C. § 119(a)-(d) or (f).

a)☐ All b)☐ Some * c)☐ None of:

1.☐ Certified copies of the priority documents have been received.

2.☐ Certified copies of the priority documents have been received in Application No. _____ .

3.☐ Copies of the certified copies of the priority documents have been received in this National Stage application from the International Bureau (PCT Rule 17.2(a)).

* See the attached detailed Office action for a list of the certified copies not received.

14)☐ Acknowledgment is made of a claim for domestic priority under 35 U.S.C. § 119(e) (to a provisional application).

a) ☐ The translation of the foreign language provisional application has been received.

15)☒ Acknowledgment is made of a claim for domestic priority under 35 U.S.C. §§ 120 and/or 121.

Attachment(s)

1) ☒ Notice of References Cited (PTO-892)
2) ☐ Notice of Draftsperson's Patent Drawing Review (PTO-948)
3) ☒ Information Disclosure Statement(s) (PTO-1449) Paper No(s) 4.5 .
4) ☐ Interview Summary (PTO-413) Paper No(s). _____ .
5) ☐ Notice of Informal Patent Application (PTO-152)
6) ☐ Other: .

DETAILED ACTION

1. Claims 25-27 are pending and under examination.

Specification

2. The disclosure is objected to because of the following informalities:

a. The first line of the specification needs to indicate the relationship between the nonprovisional applications, except for the benefit claim to the prior application in a continued prosecution application (CPA). See United States Patent and Trademark Office OG Notices: 1268 OG 89 (18 March 2003) "Benefit of Prior-Filed Application".

b. In addition, it appears that the instant application is a CIP of U.S. Serial No. 09/741,843. The instant application discloses the limitation of a variable light chain CDR3 consisting of amino acids 95-102 (see Figures 1, 4A and 5A). Prior application no. 09/741,843 does not provide support for this limitation.

Appropriate correction is required.

Claim Rejections - 35 USC § 112

3. The following is a quotation of the first paragraph of 35 U.S.C. 112:

> The specification shall contain a written description of the invention, and of the manner and process of making and using it, in such full, clear, concise, and exact terms as to enable any person skilled in the art to which it pertains, or with which it is most nearly connected, to make and use the same and shall set forth the best mode contemplated by the inventor of carrying out his invention.

4. Claims 25-27 are rejected under 35 U.S.C. 112, first paragraph, because the specification, while being enabling for a LL2 monoclonal antibody or a humanized LL2 antibody or an antigen binding fragment thereof wherein CDR1 comprises amino acids 24-40 of SEQ ID NO: 2, CDR2 comprising amino acids 56-62 of SEQ ID NO: 2, CDR3 comprising 95-102 of SEQ ID NO: 2 and the heavy chain comprises CDR1 comprising amino acids 31-35 of SEQ ID NO: 4, CDR2 comprising amino acids 50-66 of SEQ ID NO: 4 and CDR3 comprising amino acids 99-105 of SEQ ID NO: 4 wherein the antibody or antigen binding fragment thereof binds the same antigen as the non-human parent and compositions comprising such, does not reasonably provide enablement for a humanized LL2 antibody or any "fragment thereof" containing a full set of six CDRs and at least one substituted amino acid in the framework regions that does not bind antigen or the same antigen as the non-human parent as broadly encompassed by the claims. The specification does not enable any person skilled in the art to which it pertains, or with which it is most nearly connected, to make or use the invention commensurate in scope with these claims.

Factors to be considered in determining whether undue experimentation is required are summarized in Ex parte Forman, 230 USPQ 546 (BPAI 1986). They include the nature of the invention, the state of the prior art, the relative skill of those in the art, the amount of direction or guidance disclosed in the specification, the presence or absence of working examples, the predictability or unpredictability of the art, the breadth of the claims, and the quantity of experimentation which would be required in order to practice the invention as claimed.

The claims are broadly drawn to LL2 monoclonal antibodies and a humanized LL2 antibodies and fragments thereof having any amino acid substituted in the framework regions that do not bind antigen or do not bind the same antigen as the non-human parent antibody.

The specification discloses only humanized LL2 antibodies that contain both a VH and a VL chain comprising all 6 CDRs and the humanized antibodies bind antigen (see examples 6 and 7). The specification does not enable humanized LL2 antibodies, which contain all 6 CDRs and do not bind antigen or do not bind the same antigen as the non-human parent.

The claims encompass humanized LL2 antibodies and fragments thereof that do not bind antigen or do not bind the same antigen as the parent and have at least one amino acid substituted in the framework regions. The amino acid sequences and conformations of each of the heavy and light chain CDRs are critical in maintaining the antigen binding specificity and affinity, which is characteristic of the non-human parent immunoglobulin. It is expected that all of the heavy and light chain CDRs in their proper order and in the context of framework sequences which maintain their required conformation, are required in order to produce a protein having antigen-binding function and that proper association of heavy and light chain variable regions is required in order to form functional antigen binding sites. Even minor changes in the amino acid sequences of the heavy and light variable regions, particularly in the CDRs, may dramatically affect antigen-binding function as evidenced by Rudikoff et al (Proc. Natl. Acad. Sci. USA 1982 Vol. 79: page 1979). Rudikoff et al teach that the alteration of a

single amino acid in the CDR of a phosphocholine-binding myeloma protein resulted in the loss of antigen-binding function. Tramontano et al (J. Mol. Biol. 1990 Vol. 215: 175-182) teach that it is necessary to maintain certain murine framework residues (e.g. residue 71 in framework 3 can influence the structure and position of CDR2 in VH domains) in order to retain the affinity and functionality of the humanized antibody. It is unlikely that humanized LL2 antibodies as defined by the claims have the required binding function. Applicants have provided insufficient evidence or nexus that would lead the skilled artisan to predict the ability of producing a humanized LL2 antibody containing all 6 CDRs and having at least one amino acid substitution in the frameworks, resulting in a humanized LL2 antibody that retains the antigen specificity of the non-human parental antibody. The specification provides no direction or guidance regarding how to use the humanized LL2 antibodies that do not bind antigen or do not bind the same antigen as the non-human parent as broadly defined by the claims. Undue experimentation would indeed be required to produce the invention commensurate with the scope of the claims from the written disclosure alone.

Therefore, in view of the lack of guidance in the specification and in view of the discussion above one of skill in the art would be required to perform undue experimentation in order to practice the claimed invention.

Priority

5. This application repeats a substantial portion of prior Application No. 09/741,843, filed 12/22/2000, and adds and claims additional disclosure not presented in the prior application. The instant application discloses the limitation of a variable light chain CDR3 consisting of amino acids 95-102 (see Figures 1, 4A and 5A). Prior application no. 09/741,843 does not provide support for this limitation. As such, claims 25-27 are granted the filing date of 11/16/2001 of the instant application.

Claim Rejections - 35 USC § 102

6. The following is a quotation of the appropriate paragraphs of 35 U.S.C. 102 that form the basis for the rejections under this section made in this Office action:

> A person shall be entitled to a patent unless –
>
> (b) the invention was patented or described in a printed publication in this or a foreign country or in public use or on sale in this country, more than one year prior to the date of application for patent in the United States.
>
> (e) the invention was described in (1) an application for patent, published under section 122(b), by another filed in the United States before the invention by the applicant for patent or (2) a patent granted on an application for patent by another filed in the United States before the invention by the applicant for patent, except that an international application filed under the treaty defined in section 351(a) shall have the effects for purposes of this subsection of an application filed in the United States only if the international application designated the United States and was published under Article 21(2) of such treaty in the English language.

7. Claim 25 is rejected under 35 U.S.C. 102(b) as being anticipated by Pawlak-Byczkowska et al (Cancer Research. 49(16): 4568-4577, 1989, IDS filed 4/30/2003) as evidenced by Kreitman et al (Cancer Research. 53: 819-825, Feb 15, 1993).

Claim 25 recites a monoclonal LL2 antibody wherein CDR1 comprises amino acids 24-40 of SEQ ID NO: 2, CDR2 comprises amino acids 56-62 of SEQ ID NO: 2, CDR3 comprises amino acids 95-102 of SEQ ID NO: 2 and the heavy chain comprises CDR1 comprising amino acids 31-35 of SEQ ID NO: 4, CDR2 comprising amino acids 50-66 of SEQ ID NO: 4 and CDR3 comprising amino acids 99-105 of SEQ ID NO: 4.

Pawlak-Byczkowska et al teach the EPB-2 monoclonal antibody (Mab) which is also known as MAb LL2 as evidenced by Kreitman et al (see page 819, right column). Pawlak-Byczkowska et al teach EPB-2 targets B-cell lymphomas and leukemias and may be an appropriate candidate for radioimmunodetection and radioimmunotherapy of B-cell neoplasms (see pages 4568 and 4576). Since the antibody of Pawlak-Byczkowska et al is the LL2 antibody, it is inherent that the antibody has the CDRs as recited in claim 25.

8. Claim 25 is rejected under 35 U.S.C. 102(b) as being anticipated by Goldenberg et al (Journal of Clinical Immunology. 9(4): 548-564, 1991, IDS filed 4/30/2003).

Claim 25 has been described supra.

Goldenberg et al teach MAb LL2 or EPB-2 labeled with Iodine-131 for radioimmunodetection and radioimmunotherapy of B-cell lymphomas. Since the antibody of Goldenberg et al is the LL2 antibody, it is inherent that the antibody has the CDRs as recited in claim 25.

9. Claim 25 is rejected under 35 U.S.C. 102(b) as being anticipated by Kreitman et al (Cancer Research. 53: 819-825, Feb 15, 1993, IDS filed 4/30/2003).

Claim 25 has been described supra.

Kreitman et al teach MAb LL2 (also referred to as EPB-2) and LL2-Fab immunotoxins. Kreitman et al teach that *Pseudomonas* exotixin derivatives can be targeted to kill B-cell lymphoma cells by LL2 or its Fab fragment. Since the antibody of Kreitman et al is the LL2 antibody, it is inherent that the antibody has the CDRs as recited in claim 25.

10. Claim 25 is rejected under 35 U.S.C. 102(b) as being anticipated by Murthy et al (European Journal of Nuclear Medicine. 19: 394-401, 1992).

Claim 25 has been described supra.

Murthy et al teach MAb LL2 (EPB-2) labeled with technetium 99m for radioimmundetection. Since the antibody of Murthy et al is the LL2 antibody, it is inherent that the antibody has the CDRs as recited in claim 25.

11. Claim 25 is rejected under 35 U.S.C. 102(e) as being anticipated by Goldenberg M. D. (U.S. Patent 5,776,094, 102(e) date 04/07/1992).

Claim 25 has been described supra.

Goldenberg M. D. teach MAb LL2 (also known as EPB-2) and can be used to treat normal spleen cells in patients with immune diseases, lymphoma, and other diseases (see column 7, lines 36-42). Since the antibody of Goldenberg et al is the LL2 antibody, it is inherent that the antibody has the CDRs as recited in claim 25.

12. Claims 25-27 are rejected under 35 U.S.C. 102(b) as being anticipated by Leung S. O. et al (Proceedings of the American Association for Cancer Research Annual Meeting. Vol. 34, pp 481, 1993, abstract 2872).

Claims 26-27 further limit claim 25 by reciting that the LL2 antibody comprises at least one human framework and a human constant region and at least one of the human framework amino acid is substituted with the corresponding non-human amino acid.

Leung et al teach humanization of MAb LL2 by grafting the CDRs of LL2 onto human VH and VL frameworks. It is inherent that certain human framework amino acid residues are substituted with the corresponding non-human amino acid residues that are either unique to the non-human sequence or shown to interact with antigen and thus, are important to maintaining binding function. Since the antibody of Leung et al is the LL2 antibody, it is inherent that the antibody has the CDRs as recited in claim 25.

13. Claims 25-27 are rejected under 35 U.S.C. 102(b) as being anticipated by Leung S. O. et al (Molecular Immunology. 32(17-18): 1413-1427, 1995).

The claims have been described supra.

Leung et al teach humanization of MAb LL2 as a diagnostic and immunotherapeutic suitable for repeated administration and humanization minimizes or circumvents the human anti-mouse antibody response. Leung et al teach LL2 VH and Vk sequences sharing 100 % amino acid identity with SEQ ID NO: 4 and SEQ ID NO: 2, respectively wherein light chain variable region CDR1 consists of residues 24-40, CDR2 consists of residues 56-62, CDR3 consists of residues 95-102 and the heavy chain variable region CDR1 consists of residues 31-35, CDR2 consists of residues 50-66 and CDR3 consists of residues 99-105 (see Figure 1). Leung et al teach human framework regions and murine framework residues identified to have important contacts with the

CDRs by computer modeling were retained in the humanized sequence and murine framework sequences that are different from that of the human human framework residues at corresponding positions were also retained in the humanized antibody (see pages 1420 and 1423 and Figures 1 and 2).

14. Claims 25-27 are rejected under 35 U.S.C. 102(b) as being anticipated by Juweid M. et al (Cancer Research. 55(23 Suppl): 5899s-5907s, 1995).

The claims have been described supra.

Juweid et al teach humanization of the LL2 antibody wherein human EU heavy-chain framework served as the base on which CDRs from the murine LL2 heavy chain were grafted, whereas for the light chain, the human REI light-chain framework from the human kappa chain subgroup 1 was selected. Juweid et al teach that the murine framework residues considered essential in maintaining binding function based on computer modeling were retained in the humanized antibody and regions that are in close vicinity to the CDRs were conserved as much as possible (see page 5900s, left column). Since the antibody of Juweid et al is the LL2 antibody, it is inherent that the antibody has the CDRs as recited in claim 25.

Claim Rejections - 35 USC § 103

15. The following is a quotation of 35 U.S.C. 103(a) which forms the basis for all obviousness rejections set forth in this Office action:

> (a) A patent may not be obtained though the invention is not identically disclosed or described as set forth in section 102 of this title, if the differences between the subject matter sought to be patented and the prior art are such that the subject matter as a whole would have been obvious at the time the invention was made to a person having ordinary skill in the art to which said subject matter pertains. Patentability shall not be negatived by the manner in which the invention was made.

The factual inquiries set forth in *Graham* **v.** *John Deere Co.*, 383 U.S. 1, 148 USPQ 459 (1966), that are applied for establishing a background for determining obviousness under 35 U.S.C. 103(a) are summarized as follows:

1. Determining the scope and contents of the prior art.
2. Ascertaining the differences between the prior art and the claims at issue.
3. Resolving the level of ordinary skill in the pertinent art.
4. Considering objective evidence present in the application indicating obviousness or nonobviousness.

This application currently names joint inventors. In considering patentability of the claims under 35 U.S.C. 103(a), the examiner presumes that the subject matter of the various claims was commonly owned at the time any inventions covered therein were made absent any evidence to the contrary. Applicant is advised of the obligation under 37 CFR 1.56 to point out the inventor and invention dates of each claim that was not commonly owned at the time a later invention was made in order for the examiner to consider the applicability of 35 U.S.C. 103(c) and potential 35 U.S.C. 102(e), (f) or (g) prior art under 35 U.S.C. 103(a).

16. Claims 25-27 are rejected under 35 U.S.C. 103(a) as being unpatentable over Pawlak-Byczkowska et al (Cancer Research. 49(16): 4568-4577, 1989, IDS filed

4/30/2003) as evidenced by Kreitman et al (Cancer Research. 53: 819-825, Feb 15, 1993) in view of Queen et al (U.S. Patent No. 5,530,101, filed 12/19/1990) and Goldenberg et al (Journal of Clinical Immunology. 9(4): 548-564, 1991, IDS filed 4/30/2003) and Orlandi et al (Proc. Natl. Acad. Sci. USA, 86:3833-3837, 1989).

Claims 25-27 have been described supra (see items 7 and 12 above).

Pawlak-Byczkowska et al have been described supra (see item 7 of this office action). Additionally, Pawlak-Byczkowska et al teach the production and isolation of the murine monoclonal LL2 (EBP-2) antibody from ascites-grown hybridoma cells (see page 4569, left column).

Pawlak-Byczkowska et al do not specifically teach obtaining the LL2 antibody sequences from the hybridoma or humanization of the LL2 monoclonal antibody. These deficiencies are made up for in the teachings of Queen et al and Goldenberg et al and Orlandi et al.

Queen et al teach humanized antibodies comprising CDRs from non-human donor VH and VL chains and human framework regions and a human constant region and the humanized antibody binds the same antigen as the non-human donor antibody, providing the CDRs. Queen et al teach antibody humanization wherein amino acids in the acceptor sequence (human) are replaced by the corresponding amino acids from the donor sequence (non-human) if they are part of a CDR, and optional amino acid substitutions of a human framework amino acid of the acceptor immunoglobulin with the corresponding amino acid in the donor immunoglobulin if the amino acid in the human framework region of the acceptor immunglobulin is rare for that position and the

corresponding amino acid in the donor immunoglobulin is common for that position in human immunoglobulin sequences or the amino acid is immediately adjacent to one of the CDRs or the amino acid is predicted to be within about 3 Å of the CDRs in a three-dimensional immunoglobulin model and capable of interacting with the antigen or with CDRs of the humanized immunoglobulin (see columns 2-3). Queen et al teach humanization of the M195 antibody wherein the light chain CDRs comprise amino acids 24-38, 54-60 and 93-101 and the heavy chain CDRs comprise 31-35, 50-66 and 95-105 (see Table 1 in column 43). Further, Queen et al teach that positions immediately adjacent to one or more of the 3 CDRs in the primary sequence of the humanized immunoglobulin chain, the donor amino acids rather than acceptor amino acids may be selected because these amino acids are likely to interact with the amino acids in the CDRs and, if chosen from the acceptor, to distort the donor CDRs and reduce affinity (see column 14, lines 27-33). Queen et al teach that most monoclonal antibodies do not fix human complement well, are immunogenic when injected in human patients (i.e. human anti-mouse antibody response; HAMA) and humanized antibodies will "presumably have a longer half-life more similar to naturally occurring human antibodies, allowing smaller and less frequent doses to be given" (see columns 1 and 16).

Goldenberg et al have been described supra (see item 8 of this office action). Additionally, Goldenberg et al teach isolation of the murine monoclonal LL2 antibody from ascites grown hybridoma cells (see page 549, left column). Goldenberg et al teach that murine monoclonal antibodies stimulate HAMA and prevent its targeting to the

tumor and myelotoxicity can be dose limiting (see page 548, right column). Goldenberg et al teach that HAMA responses developed in some patients following administration of the LL2 monoclonal antibody (see page 552, left column). Since the antibody of Pawlak-Byczkowska et al and Goldenberg et al is the LL2 antibody, it is inherent that the antibody has the CDRs as recited in claim25.

Orlandi et al teach a general method for obtaining the VH and the VL genes and the amino acid sequence of an antibody by PCR from hybridoma cells. Orlandi also teaches primers and the use of said primers to clone DNA encoding murine variable heavy regions (see page 3833 and 3834) and the method obtained the sequences for five of the hybridomas for which it was applied.

It would have been prima facie obvious to one of ordinary skill in the art at the time the claimed invention was made to use the method of Orlandi to obtain the murine monoclonal LL2 antibody sequence from the hybridoma cells as taught by Pawlak-Byczkowska et al and Goldenberg and use the method of Queen et al to produce a humanized LL2 antibody in order to reduce HAMA, increase effector function (i.e. CDC or ADCC) and increase antibody half-life for diagnosis or therapeutic benefit of human lymphomas and leukemias of B-cell lineage.

One of ordinary skill in the art would have been motivated to and had a reasonable expectation of success to use the method of Orlandi to obtain the murine monoclonal LL2 antibody sequence from the hybridoma cells as taught by Pawlak-Byczkowska et al and Goldenberg et al and use the method of Queen et al to produce a humanized LL2 antibody in order to reduce HAMA, increase effector function (i.e. CDC

or ADCC) and increase antibody half-life for diagnosis or therapeutic benefit of human lymphomas and leukemias of B-cell lineage in view of Pawlak-Byczkowska et al and Queen et al and Goldenberg et al and Orlandi et al because Pawlak-Byczkowska et al teach the murine EPB-2 monoclonal antibody (Mab) which is also known as MAb LL2 as evidenced by Kreitman et al (see page 819, right column), which targets B-cell lymphomas and leukemias and may be an appropriate candidate for the radioimmunodetection and radioimmunotherapy of B-cell neoplasms (see pages 4568 and 4576) and the antibody can be isolated from hybridoma cells. In addition, one of ordinary skill in the art would have been motivated to and had a reasonable expectation of success to use the method of Orlandi to obtain the murine monoclonal LL2 antibody sequence from the hybridoma cells as taught by Pawlak-Byczkowska et al and Goldenberg and use the method of Queen et al to produce a humanized LL2 antibody in order to reduce HAMA, increase effector function (i.e. CDC or ADCC) and increase antibody half-life for diagnosis or therapeutic benefit of human lymphomas and leukemias of B-cell lineage in view of Pawlak-Byczkowska et al and Queen et al and Goldenberg et al and Orlandi et al because Queen et al teach antibody humanization wherein the light chain CDRs comprise amino acids 24-38, 54-60 and 93-101 and the heavy chain CDRs comprise amino acids 31-35, 50-66 and 95-105 and amino acid positions immediately adjacent to one or more of the 3 CDRs in the primary sequence of the humanized immunoglobulin chain, the donor amino acids (non-human) rather than acceptor amino acids (human) may be selected because these amino acids are likely to interact with the amino acids in the CDRs and affect affinity. Additionally,

Queen et al and Goldenberg et al teach that murine monoclonal antibodies stimulate HAMA and Goldenberg et al teach that the LL2 monoclonal antibody induced HAMA responses in some patients. Therefore, it would have been obvious to produce a humanized LL2 antibody in order to reduce HAMA, thereby allowing repeated administrations required by diagnostic and therapeutic procedures. Thus, it would have been obvious to one skilled in the art to use the method of Orlandi to obtain the LL2 antibody sequence from the hybridoma cells as taught by Pawlak-Byczkowska et al and Goldenberg et al and use the method of Queen et al to produce a humanized LL2 antibody in order to reduce HAMA, increase effector function (i.e. CDC or ADCC) and increase antibody half-life for diagnosis or therapeutic benefit of human lymphomas and leukemias of B-cell lineage in view of Pawlak-Byczkowska et al and Queen et al and Goldenberg et al and Orlandi et al.

Double Patenting

17. The nonstatutory double patenting rejection is based on a judicially created doctrine grounded in public policy (a policy reflected in the statute) so as to prevent the unjustified or improper timewise extension of the "right to exclude" granted by a patent and to prevent possible harassment by multiple assignees. See *In re Goodman*, 11 F.3d 1046, 29 USPQ2d 2010 (Fed. Cir. 1993); *In re Longi*, 759 F.2d 887, 225 USPQ 645 (Fed. Cir. 1985); *In re Van Ornum*, 686 F.2d 937, 214 USPQ 761 (CCPA 1982); *In re Vogel*, 422 F.2d 438, 164 USPQ 619 (CCPA 1970);and, *In re Thorington,* 418 F.2d 528, 163 USPQ 644 (CCPA 1969).

A timely filed terminal disclaimer in compliance with 37 CFR 1.321(c) may be used to overcome an actual or provisional rejection based on a nonstatutory double patenting ground provided the conflicting application or patent is shown to be commonly owned with this application. See 37 CFR 1.130(b).

Effective January 1, 1994, a registered attorney or agent of record may sign a terminal disclaimer. A terminal disclaimer signed by the assignee must fully comply with 37 CFR 3.73(b).

18. Claims 25-27 are rejected under the judicially created doctrine of obviousness-type double patenting as being unpatentable over claims 1-4 of U.S. Patent No. 6,187,287 B1. Although the conflicting claims are not identical, they are not patentably distinct from each other because the instant claims are drawn towards a humanized monoclonal LL2 antibody, wherein the light chain comprises CDR1 comprising amino acids 24-40 of SEQ ID NO: 2, CDR2 comprising amino acids 56-62 of SEQ ID NO: 2 and CDR3 comprising 95-102 of SEQ ID NO: 2 and the heavy chain comprises CDR1 comprising amino acids 31-35 of SEQ ID NO: 4, CDR2 comprising amino acids 50-66 of SEQ ID NO: 4 and CDR3 comprising amino acids SEQ ID NO: 4. Patent No. 6,187,287 B1 is drawn towards a humanized monoclonal LL2 antibody, wherein the CDRs of the light chain variable region of comprise CDR1 comprising amino acids 24-40 of SEQ ID NO: 2, CDR2 comprising amino acids 56-62 of SEQ ID NO: 2 and CDR3 comprising 95-103 of SEQ ID NO: 2 and the heavy chain comprises CDR1 comprising amino acids 31-35 of SEQ ID NO: 4, CDR2 comprising amino acids 50-66 of SEQ ID NO: 4 and CDR3 comprising amino acids SEQ ID NO: 4. Claims 1-4 of U.S. Patent No. 6,187,287 B1 are obvious variants of claims 25-27 of the instant application because SEQ ID NO: 2 and SEQ ID NO: 4 in the instant application share 100% amino acid identity with SEQ ID NO: 2 and SEQ ID NO: 4 in Patent No. 6,187,287 B1 and it would have been obvious to select human frameworks having the highest sequence homology to the frameworks of Vk and VH domains of LL2 in order to maintain antibody conformation and functionality

of the humanized antibody. Further, claims 1-4 of U.S. Patent No. 6,187,287 B1 are obvious variants of claims 25-27 of the instant application because it would have been obvious to substitute certain human framework amino acid residues with the corresponding non-human amino acid residues that are either unique to the non-human sequence or have potential CDR contacts and thus, are important to maintaining binding function of the humanized antibody.

19. Claims 25-27 are rejected under the judicially created doctrine of obviousness-type double patenting as being unpatentable over claims 1, 9, 20-21, 25-26 and 29-30 of U.S. Patent No. 5,789,554. Although the conflicting claims are not identical, they are not patentably distinct from each other because the instant claims are drawn towards a humanized monoclonal LL2 antibody, wherein the light chain comprises CDR1 comprising amino acids 24-40 of SEQ ID NO: 2, CDR2 comprising amino acids 56-62 of SEQ ID NO: 2 and CDR3 comprising 95-102 of SEQ ID NO: 2 and the heavy chain comprises CDR1 comprising amino acids 31-35 of SEQ ID NO: 4, CDR2 comprising amino acids 50-66 of SEQ ID NO: 4 and CDR3 comprising amino acids SEQ ID NO: 4 and any human framework or human constant region are used. Claims 1, 9, 20-21, 25-26 and 29-30 in Patent No. 5,789,554 are drawn towards humanized monoclonal LL2 antibodies. The claims in patent no. 5,789,554 are obvious variants of the claims in the instant application because the humanized LL2 light chain CDRs of SEQ ID NO: 6 are identical to the murine light chain CDRs of SEQ ID NO: 2. Likewise, the humanized LL2 heavy chain CDRs of SEQ ID NO: 8 and SEQ ID NO: 9 share 100% amino acid identity

with the murine heavy chain CDRs of SEQ ID NO: 4 and it would have been obvious to select human frameworks having the highest sequence homology to the frameworks of Vk and VH domains of LL2 in order to maintain antibody conformation and functionality of the humanized antibody. Claims 1, 9, 20-21, 25-26 and 29-30 of U.S. Patent No. 5,789,554 are obvious variants of claims 25-27 of the instant application because it would have been obvious to substitute certain human framework amino acid residues with the corresponding non-human amino acid residues that are either unique to the non-human sequence or have potential CDR contacts and thus, are important in maintaining binding function of the humanized antibody.

Conclusion

20. No claim is allowed.

21. Any inquiry concerning this communication or earlier communications from the examiner should be directed to David J. Blanchard whose telephone number through January 19, 2004 is (703) 605-1200. The examiner can be reached at (571) 272-0827 after January 21, 2004. The examiner can normally be reached at (703) 605-1200 from 8:00 AM to 5:00 PM. If attempts to reach the examiner by telephone are unsuccessful, the examiner's supervisor, Anthony C. Caputa, can be reached at (703) 308-3995. Any inquiry of a general nature or relating to the status of this application or proceeding should be directed to the receptionist whose telephone number is (703) 308-1123.

Official papers related to this application may be submitted to Group 1600 by facsimile transmission. The faxing of such papers must conform to the notice published in the Official Gazette, 1096 OG 30 (November 15, 1989). The official fax number for Group 1600 where this application or proceeding is assigned is (703) 872-9306.

Respectfully,
David J. Blanchard
703-605-1200

LARRY R. HELMS, PH.D
PRIMARY EXAMINER

Anthony C. Gupta
SPE AU 1642

JASEMINE C. CHAMBERS
DIRECTOR
TECHNOLOGY CENTER 1600